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Contrast Fractional Flow Reserve (cFFR): A pragmatic response to the call for simplification of invasive functional assessment

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ABSTRACT

Aim: To review the current approaches to simplify functional assessment of coronary stenosis with particular regard for contrast Fractional Flow Reserve (cFFR).
Methods and results: Maximal hyperaemia to assess FFR is perceived as time-consuming, costly, unpleasant for the patient and associated with side effects. Resting indexes, like Pd/Pa and iFR, have been proposed to circumvent the use of vasodilators as well as an approach based on the administration of contrast medium to induce coronary vasodilation, the cFFR. Contrast FFR can be obtained quickly, at very low cost in the absence of substantial side effects. Among these alternative indexes, cFFR shows the best correlation with FFR, reduces the use of adenosine even more than a hybrid resting approach but has not yet been tested in a randomized, controlled trial with clinical end-points.
Conclusion: cFFR represents a cheap, safe and effective alternative to FFR, able to facilitate the dissemination of a functional approach to myocardial revascularization.

1. From coronary flow reserve to fractional flow reserve

Our knowledge of coronary physiology stems from the seminal studies by Lance Gould et al. [1] who first assessed the quantitative haemodynamic relationship between lumen reduction and Coronary Flow Reserve (CFR). They studied 12 consecutive dogs who underwent a progressive occlusion of the left circumflex coronary artery inducing hyperaemia by the intra-coronary (i.c.) injection of Sodium Diatrizoate, a high osmolality contrast medium. Their data demonstrated that resting coronary flow is not altered up to a lumen diameter reduction of about 90%, whereas maximal coronary flow is limited starting from lumen reduction of about 50%. These experimental results were confirmed in humans by the same group [2], leading some years later to the attempt to use CFR in clinical practice [3,4]. However, CFR measurement was affected by technical pitfalls and several haemodynamic and pathophysiological confounders [5]. Furthermore, CFR alone cannot discriminate epicardial from coronary microvascular disease. To overcome these limitations, in 1993 Nico Pijls and Bernard De Bruyne first introduced the experimental basis of Fractional Flow Reserve (FFR) [6], clinically validated in the following years in well conducted randomized clinical trials and registries [7–9] leading to a class I recommendation for its utilization in current European guidelines [10].

FFR is the ratio between the maximal myocardial flow measured in the stenotic territory and the theoretical maximal blood flow in the same territory in the absence of the stenosis. Importantly, despite FFR being a ratio of two flows, it can be easily calculated from the ratio of two pressures (the aortic and the distal, Pd/Pa), provided that they are both measured during maximal hyperaemia. A direct relationship between coronary pressure and flow, however, may only be presumed if the resistance in the coronary circulation is constant and minimal, as theoretically is the case during maximum vasodilation [11]. The achievement of maximal hyperaemia is therefore the crucial prerequisite to assess correctly FFR.

2. Vasodilator agents for hyperaemia

The most potent stimulus to hyperaemia is reactive hyperaemia to coronary occlusion that was used in past to clinically validate CFR [12]. However the need for a more practical method to induce hyperaemia for clinical purposes lead to introduction of papaverine [13] and then of intra-venous (i.v.) adenosine [14]. I.v. administration of adenosine at 140 μg/Kg/min is considered the best combination between hyperaemia and side effects (including dyspnoea, chest pain, hypotension, flushing, anxiety and rhythm disturbances) [15,16], and for this reason it was chosen to be the hyperaemic agent in the pivotal FAME trial [7]. Nevertheless, i.v. adenosine is perceived as time-consuming and relatively costly [24]. Thus, i.c. adenosine is frequently used in the

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everyday cath-lab practice [17] in order to obtain maximal coronary vasodilation limiting systemic symptoms, costs and procedural times imposed by i.v. adenosine. In this regard, the optimal dosage for i.c. adenosine has been a matter of debate in the continuous search of a balance between a sufficient vasodilation and an acceptable rate of transient atrio-ventricular block [18–20]. For example, in the NASCI study [20], we showed that only 600 μg of i.c. adenosine achieved FFR values comparable to i.v. adenosine but at the price of a higher risk of atrio-ventricular block. More recently, Adjedj et al. [21] identified i.c. adenosine doses of 200 μg and 100 μg, respectively for left coronary artery and right coronary artery, as the best compromise between side effects and efficacy in terms of increase in flow. Nevertheless, rate of atrio-ventricular block (from 15% to 40% of cases) and suboptimal hyperaemia remained potential issues using the i.c route.

If adenosine has some drawbacks, other potentially valuable vasodilator agents are no better: use of i.c. papaverine is limited by the risk of polymorphic ventricular tachycardia [22] while i.c. sodium nitroprusside can induce severe hypotension [20,23]. These findings have been interpreted as one of the reasons for underutilization of FFR worldwide [24]. However, Toth et al. clearly demonstrated that even when FFR is made as easy as PCI in an online survey of interventional cardiologists– thus removing all time pressures and costs for both the FFR wire and hyperaemic drug – operators still do not select FFR over the angiogram [25]. Therefore, it is likely that removing or simplifying hyperaemia would not have a large effect on FFR utilization.

3. Resting indexes: Pd/Pa and iFR

In the attempt to obviate the need for the administration of vasodilator agents, attention has been paid to the possible use of resting indexes. Mamas et al. [26] investigated the relationship between resting Pd/Pa and FFR obtained during maximal hyperaemia. They retrospectively analysed 528 consecutive FFR (in which maximal hyperaemia was obtained by i.v. adenosine 140 μg/Kg/min) performed in 483 patients over a 2-year period. The authors demonstrated that resting Pd/Pa has a significant correlation with FFR and is relatively accurate in predicting a positive FFR with an AUC of 0.86. More interestingly, resting Pd/Pa values of 0.87 and 0.96 were identified as the cut-offs with, respectively, the best positive (94.6%) and negative (93%) predictive value of an ischemic FFR [7]. These results suggested that for lesions with resting Pd/Pa ≤ 0.87 and ≥0.96 the use of adenosine could be avoided with an accuracy of about 95%. However, adenosine would have been required for resting Pd/Pa values in the grey zone (0.88–0.95) in >50% of cases, with a limited spare of costs and time.

Sen and Davies proposed in 2012 the "instantaneous wave free ratio" (iFR) as a simple and potentially accurate adenosine-free index [27]. The theoretical principle of iFR rests upon the main assumption of FFR: the linear correlation between flow and pressure is valid as long as vascular resistance is constant and minimal. Sen and Davies postulated that, during the late diastole there is a short period in which flow resistance is spontaneously constant and minimal; they named such interval "wave free period" and defined iFR as the resting distal-to-proximal pressure ratio measured during the wave free period. In the original ADVISE study, the authors reported that iFR had a close correlation and agreement with FFR ($r = 0.9$, p 0.001) and an excellent diagnostic efficiency (AUC of 0.93) in predicting an ischemic FFR value, with a favourable specificity (91%), sensitivity (85%), negative (85%) and positive (91%) predictive values.

Yet, the results of the ADVISE study were not replicated in subsequent experiences and the originally hypothesized equivalent resistance between the wave-free period at rest and whole-cycle hyperaemia was disproven. In the subsequent IDEAL study from the same group of investigators, microvascular resistance was showed to be lower during hyperaemia undermining the theoretical foundations of iFR [28]. In addition Berry et al. [29] in the VERIFY study challenged the accuracy of iFR in predicting FFR especially in intermediate coronary artery stenoses, just the setting in which functional assessment is clinically important. They proposed that this lack of accuracy is probably because coronary resistance during the wave free period is at best constant but for sure not minimal. This study used non-proprietary software to estimate iFR, which may represent a limitation. For this reason, in the attempt to find a consensus on the accuracy of iFR a large collaborative group of investigators, expert in invasive functional assessment, including the inventors of iFR was formed. In the RESOLVE study, Jeremias et al. performed a large-scale, physiology core laboratory–based analysis using standardized methods and, in particular, the original algorithm developed at the Imperial College. They compared the diagnostic accuracy of iFR and Pd/Pa in predicting FFR as gold standard [30]. They found, again, that the overall linear correlation between both resting indexes with FFR was moderate ($R2 = 0.66$ and 0.69, respectively), with an overall diagnostic accuracy of 80% for both non-hyperaemic indexes (using the optimal ROC determined cut-off points of 0.90 and 0.92 to predict an FFR ≤0.80). In addition, there was no difference in sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy between the two methods in the prediction of FFR. More importantly, iFR and Pd/Pa had >90% accuracy to predict a positive or negative FFR in <65% and 50% of lesions, respectively. Accordingly, the authors concluded that, accepting FFR as the reference method (in the absence of outcome studies with iFR or Pd/Pa), this level of accuracy was insufficient to use either parameter for procedural guidance in all cases because >20% of therapeutic decisions would be discordant from FFR. On the other hand, a hybrid approach wherein Pd/Pa or iFR are accepted at the 2 outer tails of the spectrum with FFR-based decisions required in the grey area might avoid the use of hyperaemia in <50% and 65% of lesions, respectively [31,32].

Considering the suboptimal accuracy of iFR in predicting FFR, the ADVISE registry prospectively tested a iFR/FFR hybrid strategy in real world practice, using two iFR cutoffs (0.86 and 0.93) below and above which adenosine for FFR assessment could be avoided. Again, the authors demonstrated that the use of this approach could lead to spare the use of adenosine in 57% of lesions only [33]. Similar results were obtained in other registries [34–36] (Table 1).

In the opinion of the inventors of iFR, discrepancies between iFR and FFR could be dependent on the choice of FFR as the gold standard [37]. From their point of view, not only is iFR better correlated to CFR than FFR [38] but, more importantly, they argued that the 20% discrepancy between FFR and iFR results could not impact on clinical outcomes and that, consequently, iFR guidance might be non-inferior to FFR guidance. This hypothesis was tested in two large randomized clinical trials that were recently presented, the DEFINE-FLAIR and the SWEDE-HEART [39,40]. In these studies, patients with angiographically intermediate stenoses in the context of a stable ischemic heart disease or of a stabilized acute coronary syndrome after treatment of culprit vessel were randomized to an iFR-guided (using the single cut-off of <0.90) versus a FFR-guided strategy. The results of both studies concordantly found that iFR guidance was not inferior to FFR on clinical outcomes. Specifically, no significant difference was observed in the MACE rate at 12 months while both studies showed that use of iFR was associated to significantly shorter procedures with less functionally significant lesions to be treated and consequently significantly less revascularizations and stent implantations.

However, the design of these studies is questionable. Indeed, given that in 80% of stenoses iFR and FFR are concordant, no difference in outcome could be expected in the vast majority of cases. Accordingly, it was suggested that only patients who have lesions in which iFR and FFR are discordant (20% of stenoses) should have been included in a randomized, non-inferiority trial. Instead, in the present form, both studies are possibly under-powered [41]. In addition to this, the short follow up and the relatively low risk profile of the enrolled populations (and the large margin of non-inferiority assumed in the trials) impose a word of caution before replacing an extensively validated technique, such as FFR, with a relatively new index, as iFR. In fact, a recent meta-analysis